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SOME ACETYL DERIVATIVES OF THIADIAZOLIDENE: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION

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ABSTRACT: Semicarbazide used as a starting material for the synthesis of 2-phynylimino-3 amido -5 aryl /alkyl imino 1,3,4thiadiazolidine. Semicarbazide was treated with aryl/alkyl isothiocyanate to get 1-aryl-2thio bis urea (2a) and phenyl-iminocynodichloride in refluxing chloroform medium followed by basification of resulting compound (3a-g), compound (3) were converted to targeted molecule (5) by the base induced condensation followed by basification[i-vi]. The compound (5a-g) on acetylation afforded monoacetyl derivatives. Structure of all the synthesized compound have been confirmed on the basis of physical parameter, chemical test and spectral studies final compound were screened for antimicrobial activity.

KEYWORD: Thiadiazole, Heterocyclic compound, Antimicrobial Activity, Biological effect, Semicarbazide.

INTRODUCTION

Thiadiazolidine derivative which belong to the N-containing heterocyclic compound. When a ring is just composed of carbon atoms it is referred to as a homocyclic compound however when a heterocyclic ring contains other chemicals such as nitrogen, oxygen, or sulphur it is called a heterocyclic compound[vii-xii] . Thiophene, furan, and pyrrole in the past year it has been discovered that there exist several thiadiazole compounds such as 1,3,4-thiadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, and 1,2,5-thiadiazole that include nitrogen in different positions and the basic ring. 1,3,4-thiadiazole are the fused heterocyclic ring compound with a variety of biological actions, including diuretic, antidepressant, antibacterial, anti-inflammatory and antifungal properties. Medicinal chemist synthesized a variety of thiadiazolidene compound with different biological activities by installing various active groups using developing synthetic method. Numerous patents have been issued on the synthesis and use of 1,3,4 thiadiazoles as fungicidal, herbicides, Insecticides, bacteriocides, dyes, lubricant additives and vulcanization accelators[xiii]. The literature review showed that the thiadiazole nuclei have antimicrobial, antinflammatory, anticancer, antituberculor, analgesic etc.

MATERIAL AND METHOD:

Melting points of all synthesized compounds were taken in open capillaries and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 1300 FT IR spectrometer and 1H NMR were determined on a Bruker WM-400 (400 MHz FT NMR) spectrometer using TMS as internal standard using $CDCl_3$ and DMSO as solvent. Purity of compounds was checked by TLC using silica gel-G plate as adsorbent. The reagent used in the synthesis of 2-arylimino-3-amido-5-phynylimino-1,3,4thiadiazolidines have been prepared.

SCHEME FOR SYNTHESIS:

The literature survey revealed that thiadiazole moiety is an imperative heterocyclic system with different and diverse biological activities. Therefore the objective was to prepare different thiadiazole derivatives and evaluate them for their antimicrobial, analgesic, antioxidant, anti-inflammatory and antihelmintic. The synthesis of 1,3,4-Thiadiazoles derivatives is attracting attention of researchers because it has multitudinous biological activities as discussed earlier. Therefore, synthesis of different derivatives of 1,3,4-thiadiazole has been done and was evaluated for anti-microbial activity.

Synthesis of 1-aryl-2 thio-bis urea(2):

Semicarbazide (0.01) and aryl /alkyl isothiocynate (0.01mole) dissolved in minimum amount of chloroform(10ml). The reaction mixture was heated under reflux for 2 hours. After cooling the reaction mixture the product separated out as crystal was filtered, washed with water dried and recrystallised from absolute alcohol .yield 82%, m.p 180^{0}C **.**calcd. for $C_8H_9N_4SOCl$ (197), N, 28.52; S, 16.33. Found: N, 27.73; S, 16.53 %. IR (KBr, cm^{-1}): 3370, 3410 (NH), 3018 (Ar-H), 1587-1446 (C=N), 1125 (C=S). 1H NMR, (DMSO, δ): 8.7 (s, 1H, CO-NH), 7.56-8.0 (m, 4H, Ar-H), 5.7, 2H, NH_2).

Synthesis of 2-phenylimino-3-amido-5 -arylimino-1,3,4 thiadiazolidines:

A portion of 1-phenyl-2-thio bis urea (2) (0.01mole) was dissolved in minimum amount of chloroform(20ml).To this solution phenyliminoisocynodichloride (0.01mole) in chloroform was added. The reaction mixture was heated under reflux for 3-4 hrs. After cooling the product separated out as a crystal was filtered washed with water, dried and recrystallized from absolute alcohol and identified as monohydrochloride of 2 (phenylimino 3-amido-5-phenylimino 1,3,4 thiadiazolidene(3) yield74% m.p 150^{o}C.On basification with dilute ammonium hydroxide solution afforded a free base (**4a**)from ethanol m.p141^{o}CCalcd.for C_{15} $H_{12}H_5OSCl$. C, 52.01; H,2.91;N,21.00;S,9.00, (Found:C,52.09;H,3.47;N,20.23;S,9.24%) IR; (KBr,cm^{-1})3390-3450 (N-H Stret.), 1614(C=N,Stret.) 1538 (Ar C=C Stret.), 1334(C-H Stret.) ,750(C-S Stret.),; 1HNMR (DMSO, δ) 6.0(s,2H,N-H), 9.6-10.0 (m,2H,-$CONH_2$,) 7.2-7.6(m,9H,Ar-H) **(4b),** m.p142^{o}C .Calcd. for C,57.87; H,4.18; N,22.50; S,10.28% (Found:C,57.43;H,4.10; N,22.23; S,10.11;), (**4c),** m.p 148^{o}C Calcd. for C,59.07; H,4.61, N,21.53; S,9.84% (Found:C,58.91; H,4.20; N,21.02; S,9.50%),(**4d),;** m.p149 ^{o}C Calcd. For C,59.25;H,4.62,; N,21.60,; S,9.87% (Found;C,59.30;H,4.40;N,22.01;S,10.00)**, (4e),** m.p 202^{o}cCalcd.for C,59.25**;** H,4.62; N,21.60;S,9.87% (Found:C,59.08; H,4.80; N,21.30; S,9.30),**(4f),** m.p 62^{o}C Calcd. for C,59.25; H,4.62; N,21.60; S,9.87% (Found:C,59.60; H,4.40; N,21.40; S,9.50**), (4g);** m.p108 ^{o}C Calcd. For C,53.60; H,5.84; N,24.05.; S,10.9% (Found:C,54.00; H,5.32; N,23.92; S,9.95) On the basis of above chemical properties and spectral data. The compound (5) has been assigned structure(2-phenylimino-3 amido-5-phenylimino 1,3,4thiadiazolidine.The other compound (**4b-g**) were prepared by extending the above reaction to other 1-aryl-2thiobisurea (**2b-g**) the related 1,3,4 thiadiazolidine were isolated in good yield.

Synthesis of 2(phenylimino)-3-amido-4acetyl-5-phenylimino1,3,4 thiadiazolidine:
2-phenylimino-3-amido-5-arylimino-1,3,4 thiadiazolidines (4) and acetic anhydride (0.01mole) were refluxed in glacial acetic acid (10.0ml) for 1.5 hrs. The reaction mixture was cooled it was filtered and excess of solvent was removed under reduced pressure .The separated solid was filtered, washed and recrystallised from ethanol yield 72% m.p192^{0}C Calcd, for $C_{17}H_{14}N_5O_2SCl$,; C,52.62;H,3.58;N,18.06; S,8.25; Found; C,52.30; H,3.23; N,18.32; S,8.20; (KBr, IR);3390-3410(N-H Stret.); 1601(C=N Stret.); 1308 (C-N Stret.);1678 (C=O Stret.); 750 (C-S Stret.); 1HNMR ($CDCl_3$,δ);2.05 (s,3H,-$COCH_3$);7.2-7.5(m,9H,Ar-H).

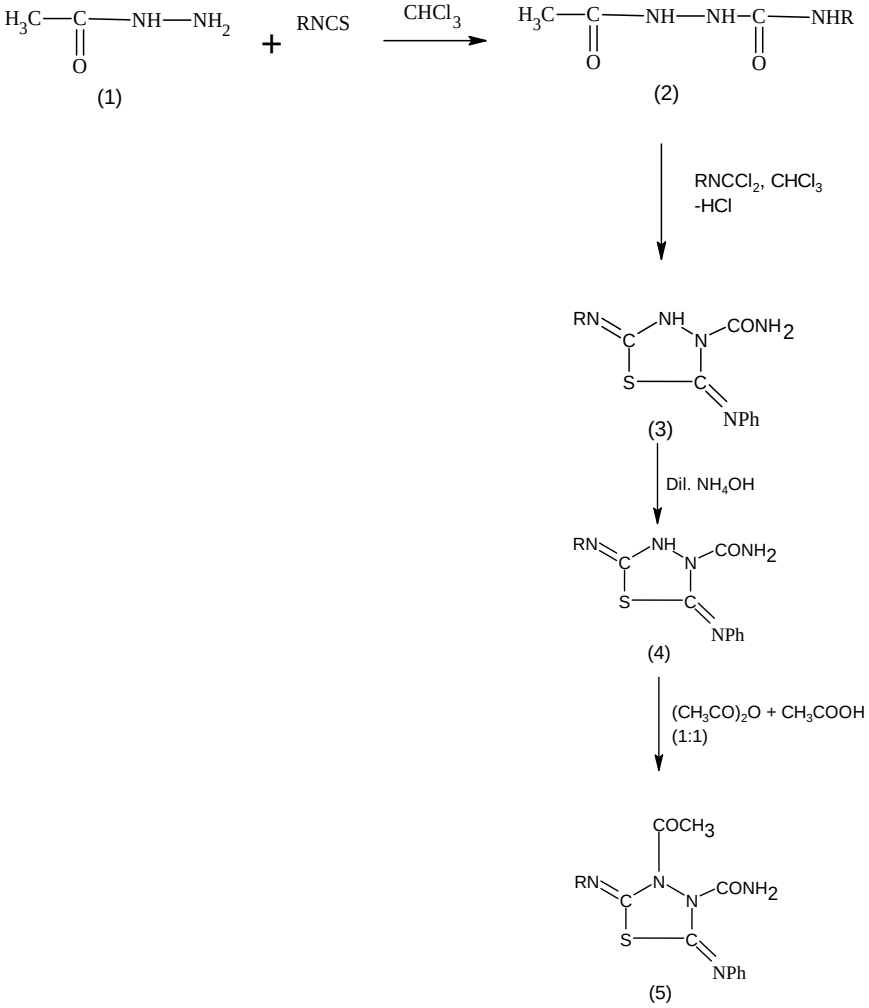

Table.1.
Physicochemical properties of the substituted 2-phenylimino-3-amido-5-arylimino -1,3,4 thiadiazolidines derivatives

Compound name	Molecular formula	Percentage Yield	M.P^{0}C	Elemental analysis Found (Calcd.)			
				C	H	N	S
5a	$C_{17}H_{14}N_5O_2SCl$	72	190	52.30 (52.62)	3.23 (3.58)	18.32 (18.06)	8.20 (8.25)
5b	$C_{17}H_{14}N_5O_2SCl$	62	107	52.30 (52.62)	3.38 (3.58)	17.80 (18.06)	8.06 (8.25)
5c	$C_{17}H_{15}N_5O_2S$	69	191	56.21 (56.30)	4.01 (4.39)	20.10 (20.52)	9.52 (9.38)

5d	$C_{18}H_{17}N_5O_2S$	68	110	58.40 (58.85)	4.20 (4.63)	18.97 (19.07)	8.52 (8.71)
5e	$C_{18}H_{17}N_5O_2S$	72	140	58.58 (58.85)	4.40 (4.63)	19.40 (19.07)	8.50 (8.71)
5f	$C_{18}H_{17}N_5O_2S$	70	108	58.63 (58.85)	4.40 (4.63)	18.90 (19.07)	8.57 (8.71)
5g	$C_{15}H_{19}N_5O_2S$	69	160	54.42 (54.05)	5.73 (5.90)	20.95 (21.02)	9.50 (9.60)

Table 2. Interpretation of IR and NMR Spectral Values

Compound name	IR Spectra value cm^{-1}	1H NMR Spectra values ppm
5a	3390-3450,NH-Str.;1601,C=N Str.;1308,C-N Str.;1678C=O,Str.;750C-S Str.	7.4 2H, Ar-H; 7.96 2H, Ar-CH; 7.00 2H, Ar-CH; 7.2 2H, Ar-CH;2.05,3H,C0CH_3
5b	1686,C=O Sytr.;1595,C=N,Str.;1312,C-N Str.701,C-S	8.05,1H,CH=N,7.21-7.60,9H,Ar-H;3.85,3H,O-CH_3;2.05,3H,CO-CH_3
5c	1684,C=O;1595,C=N;1306,C-N;697,C-S	8.19,1HCH=N;,7.06-7.62,9H,Ar-H;2.2,3H,CO-CH_3
5d	1605,C=NStr.; 3327, NH-str; 3086, Ar-CH-str; 1300, C-N str; 625, C-S-str.1666,C=OStr.	8.56 2H, Ar-CH-str; 7.60 2H, Ar-CH- str; 6.48 2H, Ar-CH-str; 6.29 2H, Ar- CH-str; 5.07 1H; Ar.H Str.;2.07,3H,CO-CH_3
5e	1609, C=N- str; 3385, NH-str; 3086, Ar-CH-str; 1300, C-Nstr; 729, C-S-str.;1675,C=O,	8.61 2H, Ar-CH-str; 7.63 2H, Ar-CH- str; 6.21 4H, Ar-CH-str;; 4.12 1H, NH;2.06,3H,-CO-CH_3
5f	3251, NH-str; 3086, Ar-CH-str; 1300, C-Nstr; 651, C-S-str.;1607,C=N Str.;1673,C=OStr.	8.65 2H, Ar-CH-str; 7.60 2H, Ar-CH- str; 7.18 2H, Ar-CH-str; 6.35 2H, Ar- CH-str; 2.05,3H,CO-CH_3
5g	3288, NH-str; 3086, Ar-CH-str; 1710, C=O-str; 1300, C-Nstr; 651, C-S-str.;1610,C=N Str.	9.20 ,2H, Ar-CH; 8.26 1H, NH; 7.96 2H, Ar-CH; 7.18 2H, Ar-CH; 6.35 2H, Ar-CH; NH; 2.06,3H,CO-CH_3

RESULT AND DISCUSSION:

The sequence of the reaction employed for the synthesis of title compound is outlined in scheme 1. The physicochemical data and spectral data of the different synthesized compound are given .The mixture of semicarbazide and phenylisothiocyanate converted 1 aryl -2 thio bis urea(2).The purity of compound was confirmed by melting point TLC and structure was confirmed by chemical test IR and 1H NMR spectral data ,IR Spectra showed the characteristic peak.IR Spectra showed the characteristic peak, CH-Stret.at 3075 cm^{-1}, C-O at 1179 cm^{-1}, NH-Stret,at 3222cm^{-1}, C=C at 1480 cm^{-1}.This 1-aryl-2-thiobisurea was reacted with phenyliminoisocynodichloride gave 2-phenylimino-3-amido-5 -arylimino-1,3,4 thiadiazolidene (5).The purity of this compound by melting point .TLC and structure was confirmed by IR,1HNMR and Mass spectral data.IR Spectra showed the characteristicpeak NH-Stret. at 3390-3450,C=N Stret.at 1614,Ar C=C Stret.at 1538,C-N Stret.at 1334,C-S Stret.at 750cm^{-1}. This 1,3,4 thiadiazolidine treated with acetic anhydride and glacial acetic acid gave 2-phynylimino-3amido-4 acetyl-5-arylimino-1,3,4 thiadiazolidine (6). The purity of compound was confirmed by melting point, TLC and structure was confirmed by IR,1HNMR and Mass

spectral data.IR Spectra showed the characteristic peak of NH-Stret.at 3390-3450,C=N stret. at 1601,C-N Stret. at 1308,C=O Stret.at 1678,C-S Stret.780cm^{-1}.The other compound (5a-g) were prepared by extending the acetylation reaction to other compound (5a-g) and gave the title compound (5a-g).

BIOLOGICAL ACTIVITY:

A number of new 1,3,4 thiadiazolidene derivatives were synthesized and evaluated to their antibacterial and antifungal activity [xiv]. The use of standardised settings to restrict microbial development can serve as a means of showing the therapeutic efficacy of antibiotics. Any minor modification to the antibiotics molecule that might escape detection by a shift will expose chemical processes in the antibacterial action and as a result microbiological tests are highly helpful in clearing up any uncertainty about potential changes in strength of medications and their preparation. The foundation of a microbiological assay is a contrasting the growth-inhibition mechanisms of microbes using precisely calibrated amounts of the antibiotics that will be looked at in that generated by known concentration of a customary method of preparing the antibiotic with a recognized behaviour [xv].

The cylinder-plate approach relies on the antibiotic spreading from a vertical cylinder through an agar layer that has solidified in a Petri dish or dish to the extent necessary for the growth of the addition of new microorganisms is totally avoided in a zone surrounding the solution-filled cylinder concerning the antibiotic. The recently produced substances in vitro efficiency was evaluated bactericidal efficacy against four bacteria, such as *E.coli,S. aureus, P. vulgaris B. subtilis, Shigella* for gram + ve and gram-ve strains and at utilizing concentrations of 100, 200, and 300 μg/ml. Ciprofloxin as an antifungal and standard reference action in opposition to *A. niger* at mg/ml of 100concentration utilizing the reference of the control.

Convention for antimicrobial Activity:

The sterilized (autoclaved at 120°C for 30 min) nutrient agar medium (40-50°C) was inoculated (1 to 100 ml) with the suspension of microorganisms and mixture was transferred to sterile petri dishes and allowed to solidify [xvi]. Specified concentration solution of synthesized compounds and standard were placed on surface of the agar plates. The plates were left for 1 hr at room temperature as period of pre incubation diffusion to minimize effects of variations in time between applications of different solutions. The plates were incubated at 37°C for 18 hr and observed for antibacterial activity. The diameters of zone of inhibition were measured and compared with that of standard, the values were assessed.

Table 3:

Antibacterial activity of 2-phenylimino-3-amido-5-arylimino -1,3,4 thiadiazolidines substituted derivatives

Organism	Zone of inhibition (diameter) in mm						
	5a	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**
P. valgaris	+	+++	++	++	+	++	+
B. subtilis	-	+	-	+	-	+	-
E. coli	+	++	++	++	++	-	+
S. aureus	++	+++	++	++	+	++	++
Shigella	+	++	+	+	++	+	+

(-) = Inactive (12mm and less)
(+) = Weakly active (13-16 mm)
(++) = Moderately active (17-20 mm)
(+++) = Highly active (21mm and above)

Inhibition zones of the Compound (5b) is having moderate to high activity. It is highly active against *S. aureus*. All the compounds are having high activity against *S. aureus* and most of them are inactive against *B. subtilis*. These compounds showed moderated activity against *E. coli* and *Shigella*.

Convention for Antifungal activity:

The antifungal activity of all of the compounds listed above (5a-5g) was determined using the paper disc method. The paper discs used were 6 mm in diameter and were soaked in a 1 and 2% solution of the derivatives in DMF. The fungus being examined was *A. niger*. The zones of inhibition were measured following a 48-hour incubation period at 37°C. Compounds (5c) and (5e) showed great action against *A. niger*, while other compounds showed significant activity.

Table3. Antifungal activity of 2-phenylimino-3-amido-5-arylimino -1,3,4thiadiazolidines substituted derivatives

Organism	Zone of inhibition (diameter) in mm							
	Concentration	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**
A. niger	**1%**	-	+	+++	++	+++	-	+
	2%	+	+	+++	+	++	+	-

CONCLUSION:

1,3,4-Thiadiazole, a well-known heterocyclic offers a wide range of bioactivity and pharmacological characteristics. One of the most significant areas in medicinal chemistry is the development and discovery of new 1,3,4-thiadiazole moiety. In conclusiona series of novel 1, 3, 4-thiadiazole derivatives were synthesized and the structures of the entire compounds were confirmed by recording by their IR, 1H NMR and Mass spectra. , we feel that the preliminary in vitro activity results of this class of compounds may possess potential for design of future molecules with modifications on the aryl substituent's All the synthesized compounds showed moderate activity againstbacteria . In particular, the compound (5b) showed good anti-bacterial compound such as (5c) and (5e) showed great action against fungi. While other compound showed significant activity.Thereforethe detailed literature survey and screening studies have demonstrated that the newly synthesized compounds properties. Hence, it is concluded that there exists expansive scope for the medicinal chemists to further study in this class of compounds and used for the treatment of various types of deadly microbial infections.

DECLARATION OF INTEREST

The authors state no conflicts of interest.

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